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Auditory Verbal Hallucinations in Schizophrenia

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AUDITORY VERBAL HALLUCINATIONS IN SCHIZOPHRENIA

By:

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A thesis submitted to the faculty of the University of Mississippi in partial fulfillment of
the requirements of the Sally McDonnell Barksdale Honors College

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Abstract

The primary auditory cortex being linked to the AVHs could be due to it being overly sensitive when being stimulated by processing found internally, opposing to outward stimulation. The 173 individuals who were available for both structural data and resting state, 83 were found to have schizophrenia or schizoaffective. Resting state echo planar image (EPI) volumes had 32 slices of 4mm 64x64 matrix with 4mm thickness (voxel size = 3x3x4mm), with repetition time (TR) of 2000ms and echo time (TE) of 29ms. A total of 150 volumes (5 minutes) were used in the analysis. The auditory cortex in the SZ group showed significantly weaker connectivity to the right supracalcarine cortex, left lingual gyrus, and right precuneus cortex and significantly stronger connectivity to the right caudate.

I dedicate this paper to my parents. Thank you for always being there for me, supporting me, and loving me through it all. I couldn't have gotten where I am today without you both. This one's for y'all.

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Introduction

Auditory verbal hallucinations (AVHs) have a way of making the patient feel like they are actually hearing the auditory stimulant rather than seeing pictures, images, or memories from the past. This phenomenon has lead researchers to believe that the primary auditory cortex plays a critical role (Kristiina et al. 2013). The primary auditory cortex being linked to the AVHs could be due to it being overly sensitive when being stimulated by processing found internally, opposing to outward stimulation. This finding can lead one to assume that the primary auditory cortex, when it is scaled back, will not activate to outward sounds which leads to the AVH (Kristiina et al. 2013).

Neuroimaging studies have been conducted to examine brain regions that are activated during AVH. The auditory cortex was one of the regions that were activated during AVHs, suggesting that the individual is experiencing sensation of hearing. The primary auditory cortex has been shown to be activated during lip-reading and imagination, showing that the external stimuli are not necessary for the primary auditory cortex to be activated. The auditory cortex in schizophrenia may be sensitized.

Postmortem studies have shown that the auditory cortex neurons have had morphological alterations in patients that have schizophrenia. AVH, when in response to actual outer stimuli, are used as one of the most recognized symptoms of schizophrenia (American Psychiatric Association, 1994). During the AVH, the primary auditory cortex in the dominant hemisphere was seen as being active (Dierks et al., 1999). This suggests that there when there is an AVH there is also a language-related process (Stephane et al., 2001). This notion is reinforced by the finding that when hallucinating, schizophrenic

patients have changes in the language-related areas, specifically in the white matter fiber tract that is connecting those areas (Hubl et al., 2004).

Processing deficits when dealing with auditory sensory matters, have been found to be in direct correlation with gray matter loss in the Heschl's gyrus (Salisbury et al., 2007). Gray matter has been shown to be lost at a greater amount when the patient is found to have had schizophrenia for a longer amount of time. This could be linked to a long term use of antipsychotic medications (Vita et al., 2012).

Studies have shown that when there is a reduction in the auditory cortex volume, there is a correlation with auditory hallucinations in patients with schizophrenia. Auditory hallucinations have been linked to having a thinner cortex, but not a smaller surface area of the left Heschl's gyrus (Mørch-Johnsen et al. 2017). Changes in the auditory cortex is strongly indicated. The auditory pathway has been linked to sending sound signals to the cochlea, leading to the hallucinations being heard as though the sound was coming from outside of the ear (Ikuta et al. 2015).

Schizophrenia has shown to have stronger connectivities of the Nucleus Accumbens (NAcc) which can be associated with hallucinations (Rolland et al., 2015). This has lead to the association between the NAcc and visual integration of speech into schizophrenia (Szyck et al., 2009). Sartorius et al. found that hallucinations within the first month of symptoms with schizophrenia surpasses 70%. 25-30% of the patients are non-responsive to medication and in return are having trouble living everyday life (Shergill et al .,1998; Copolov et al ., 2004).

Examining functional connectivity of the brain provides knowledge that would not be available otherwise. The brain is a vast network filled with connections that have

been studied extensively. Cognitive deficits have been shown in schizophrenia, even before the official diagnosis or the first sign of psychosis (Brewer et al., 2016). A genetic factor has been linked to the cognitive deficits found in patients with schizophrenia. Their family members have been shown to also have the cognitive deficits that are seen in the patients (Snitz et al., 2006). These cognitive deficits are seen in daily life (Bowie et al., 2006) and show no signs of being related to any other of the symptoms typically found in schizophrenia (O’Leary et al., 2000). The cognitive deficits can be linked to memory, processing speeds, and executive functioning (Mesholam-Gately et al., 2009, Reichenberg and Harvey, 2007). Despite that the auditory cortex has been shown to be affected in schizophrenia, it remained unclear whether schizophrenia exhibits different functional connectivity. In this study, we tested functional connectivity of the auditory cortex, using resting state functional MRI data of individuals with and without schizophrenia.

Materials and Methods

Data Acquisition

The Center for Biomedical Research Excellence in Brain Function and Mental Illness (Çetin et al., 2014) was where the data for the MRI Images, demographics, and clinical data were obtained from Collaborative Informatics and Neuroimaging Suite. (<http://coins.mrn.org/>).

Among the 173 individuals who were available for both structural data and resting state, 83 were found to have schizophrenia or schizoaffective. (hereafter SZ group,

37.31±13.97 years old). This was based on the Structured Clinical Interview for DSM-IV for Axis 1 DSM-IV Disorders (First et al., 1998). 90 of the individuals were non-psychiatric age-matched controls (control group, 37.51±11.40 years old). Individuals that were found to have bipolar disorder were excluded (9 individuals in total)

Resting state echo planar image (EPI) volumes had 32 slices of 4mm 64x64 matrix with 4mm thickness (voxel size = 3x3x4mm), with repetition time (TR) of 2000ms and echo time (TE) of 29ms. A total of 150 volumes (5 minutes) were used in the analysis. High-resolution structural T1 volume was acquired as 176 sagittal slices of 256mm x 256mm with 1mm thickness (voxel size = 1x1x1mm, TR=2530ms and TE=3.25ms).

Data Processing

Data preprocessing and statistical analyses were conducted using FMRIB Software Library (FSL,) as well as Analysis of Functional NeuroImages (AFNI). The anatomical volume for each subject was skull stripped, segmented (gray matter, white matter and CSF), and registered to the MNI 2mm standard brain. First four EPI volumes were removed. Transient signal spikes were removed by de-spiking interpolation. To correct head motion, the volumes were linearly registered to the then first volume, through which six motion parameters and displacement distance between two consecutive volumes were estimated. Each of the resting state volumes was regressed by white matter and cerebrospinal fluid signal fluctuations as well as the six motion parameters. After smoothing with a 6mm FWHM Gaussian kernel, the volumes were resampled, spatially transformed and aligned to the MNI 2mm standard brain space. Through this registration,

12 affine parameters were created between rs-fMRI volume and MNI152 2mm space, so that a seed ROI can later be registered to each individual rs-fMRI space.

To perform scrubbing where the volumes with excess motion are removed, as a displacement distance between two EPI volumes, the root mean square deviation was calculated from motion correction parameters, at an $r=40mm$ spherical surface using FSL's *rmsdiff* tool (Power et al., 2012, 2015). Volumes whose displacement distance exceeded the threshold (0.3mm) were removed from further statistical analyses (Siegel et al., 2014).

The primary auditory cortex was defined by extracting Heschl's gyrus from the Harvard-Oxford atlas. The mean EPI signal within each of the ROI was first estimated for each volume. The correlation between these two mean values for the two ROIs across the series in each subject was then calculated and transformed to Z-scores.

The SZ and control groups were compared by *randomise* script in FSL. Statistic images were estimated where clusters were determined by the statistical threshold of $p < 0.001$ (family-wise error-corrected) and minimal voxel number in a cluster of $k > 30$.

Results

The auditory cortex in the SZ group showed significantly weaker connectivity to the right supracalcarine cortex, left lingual gyrus, and right precuneus cortex and significantly stronger connectivity to the right caudate (Table 1).

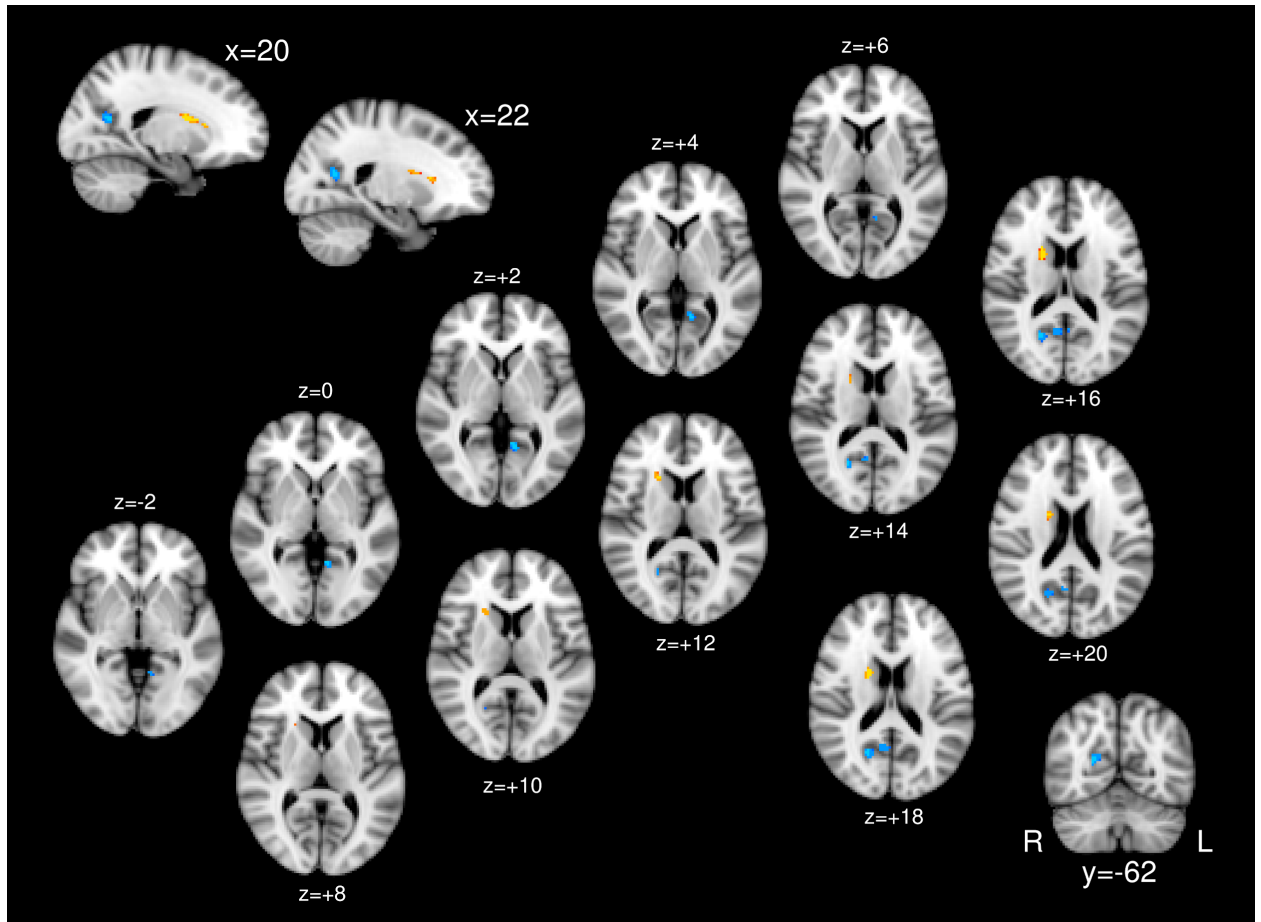


Figure 1: Regions that showed lower or higher connectivity with the auditory cortex in the SZ group compared to the control group.

Voxels (<i>k</i>)	Peak MNI coordinates			Region
	x	y	z	
<hr/>				
SZ < control				
50	22	−62	14	Right Supracalcarine Cortex
39	−10	−54	0	Left Lingual Gyrus
37	10	−58	14	Right Precuneus Cortex

SZ > control

82	22	18	12	Right Caudate
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Table 1. Summary of the regions that showed lower or higher connectivity with the auditory cortex in the SZ group compared to the control group.

Discussion

In this study, functional connectivity of the auditory cortex in schizophrenia was examined. The right caudate showed stronger, and the right supracalcarine, left lingual and right precuneus cortex showed weaker connectivity with the auditory cortex in schizophrenia.

Supracalcarine, lingual and precuneus (together). Multi-sensory integration may be affected in schizophrenia (Kiparizoska 2017). It has been found that there is a lack of connectivity between the auditory, olfaction, and visual processings regions of the brain

in patients with schizophrenia, when compared to their healthy counterparts. In particular, the Piriform cortex functional connectivity to the visual cortex is significantly less in those with schizophrenia. While connectivity between olfactory and visual cortices has been shown to be weaker in schizophrenia, our results showed connectivity between auditory and visual cortices are weaker. It supports the idea that sensory integration is reduced in schizophrenia.

The supracalcaline cortex includes the primary visual cortex. Our results indicate disconnectivity between the primary auditory cortex and visual cortex. It is suggested that these two sensory modalities are less communicating in schizophrenia, which may potentially account for such symptoms as hallucinations where one modality takes false input by ignoring other sensory inputs.

The precuneus cortex has been suggested to be the core of the Default Mode Network (DMN) (Utevsky et al. 2015). The precuneus cortex has shown to have increased activation during memory retrieval (Maddock et al., 2001), reward outcome monitoring (Hayden et al., 2008), and emotional stimulus processing (Maddock et al., 2003). These show that there is functional connectivity between the Default mode network (DMN) and the precuneus cortex. When in a heighten task state the precuneus cortex exhibits connectivity patterns that can discriminate task state. With the precuneus cortex being a central node in the brain and comprising a core region of the default mode network, which is important for complex cognition and behavior, it has been shown to have decreased activation during externally driven tasks (Raichle et al., 2001; Fransson, 2005). The precuneus cortex requires about 35% more glucose than any other brain region (Gusnard and Raichle, 2001). The amount of connectivity between the precuneus

and higher association regions suggests that the precuneus is crucial in the integration of internally and externally driven information (Cavanna and Trimble, 2006). The amount of connectivity between the precuneus and the default mode network is directly relational to the amount of engagement is needed for one's surroundings (Leech et al., 2011). Disconnectivity of the precuneus corresponds to the symptoms of schizophrenia where interactions with one's surroundings are disrupted.

The lingual gyrus is a part of the brain that is responsible for visual processing and analyzing logical order. The left lingual gyrus has been found to activate when trying to memorize an image and when the memorization is trying to be maintained (Kozlovskiy et al. 2014.). The lingual gyrus has been linked to recognition and identification of words, more specifically letters (Mechelli. A.. Humphreys. G. W.). Visual memory dysfunction, visuo-limbic disconnection, and impaired visual memory have been linked to problems or damage with the lingual gyrus. Retrieval fluency in children has also been linked to the functionality of the lingual gyrus. The lingual gyrus has been linked to the hippocampus in the brain. This was found through a study where children were asked to work through critical thinking problems. The study found that the lingual gyrus was linked not to the actual problem solving itself, but the recollection of the data they needed to use when solving the problem. (*Pr Denis Ducreux 2014-2015*) Dysfunction of the lingual gyrus may account for certain symptoms of schizophrenia where visual and logical processing are affected.

It has been found that there is lower functional connectivity from the piriform cortex to the right intracalcarine cortex, left intracalcarine cortex, right planum temporale, and left occipital lobe. The intracalcarine cortex is found in the occipital lobe and is the

main input site of signals coming from the retina (Lali et al. 2016). The lack of connectivity relating to the piriform cortex and the intracalcarine cortex could be related back to the patients with schizophrenia showing positive symptoms. The connectivity that has been linked between the right planum temporale and the piriform cortex has been very low. The right planum temporale is for meaning etc, based on auditory or visual input. The right planum temporale plays a very important role in stimulus selection during dichotic listening (Hirnsstein, Westerhouse). This suggests that the right planum temporale is involved in stimulus driven auditory processing and the lower co-activation of the two could be a cause for the patient to show positive signs for schizophrenia. The left occipital lobe and the piriform cortex were found to have the lowest sign of difference between patients who have schizophrenia versus the people who do not. This could be linked back to the left occipital lobe being extremely active and it not needing the same amount of connectivity that the previous regions of the brain need. The four above area's have all been found to be connected to the piriform cortex when being co-activated. This can suggests a intense interconnectivity which, in people that have schizophrenia, can be less co-activated and then lead to more positive symptoms than those found to not have schizophrenia (Kiparizoska, Sara 2016).

When making a perceptual decision, the single-neuron activity in caudate encodes multiple computations. Bias in the beginning process of decision making, accumulation of evidence, and seeking the standard of the evidence, has all been found in single-neuron activity in the caudate. This could explain that when involving perceptual decisions, the corticofugal and corticobasal ganglia pathways could involved both sensory and nonsensory factors that assess perceptual decisions. This could be two fulfill a certain

behavioral goal. When talking about decision making there has been three main links to being able to make a flexible decision. The first is how the subject is able to gather evidence about the decision. (Roitman and Shadlen, 2002; Smith and Ratcliff, 2004). The second is whether the subject can become confident about the reward or negative outcome of the decision (Sutton and Barto, 1998; Kepecs et al., 2008; Kiani and Shadlen, 2009). The third element is when the subject is making the decision and can comprehend what other factors are going to influence the decision process, whether through evaluation of the process as a whole or other factors (Carpenter and Williams, 1995; Voss et al., 2004; Bogacz et al., 2006; Diederich and Busemeyer, 2006). The caudate is involved in all three of these elements.

Patients with schizophrenia have been found to have weaker specialization in the left caudate nucleus. In relation to that, the right caudate nucleus has been found to be the exact opposite pattern. The cortical regions that are in connectivity with the caudate nucleus have been found to be disrupted in patients with schizophrenia (Mueller et al. 2015). Cognitive ability, language finding, and task allowance, have all been linked to a biomarker in schizophrenia that is less susceptible to the above outcomes of variations. Obscure nucleus specialization at the beginning of schizophrenia when being linked to genetic variants could indicate that the patient has schizophrenia earlier than previous tests could. This could also lead to being able to see how risk genes directly correlate with neurodevelopmental changes that would eventually lead to the onset of schizophrenia symptoms (Mueller et al. 2015).

It is the limitation of this study that we do not have information about the hearing status in the participants, except that they are not reported to be hearing impaired. The

problem that can come with not knowing the patient's hearing status are not being able to know if the Deaf or hard-of- hearing have a different experience when it comes to the AVHs. Not knowing the extent to how well the patient can hear can affect the study by not allowing us to be able to make a correlation with the outside hearing that the patient might have heard from previous encounters and if this could be related back to the sounds that they are experiencing.

In conclusion, this study found that patients who are experiencing AVHs have an auditory cortex that is sending sound to the cochlear without the presence of external stimulation. Cognitive deficits can be linked back to finding it hard to remember things, problems with daily functional activities, and difficulties processing in higher order thinking . The lack of connectivity of the piriform cortex and the intracalcarine cortex are shown in patients exhibiting positive schizophrenia symptoms.

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